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3.2.P.8. STABILITY

3.2.P.8.1. STABILITY SUMMARY AND CONCLUSION

The initial commercial shelf life of the BNT162b2 drug product is 6 months when stored at the intended storage condition of -90 to -60 °C. The initial shelf life is based on the currently available data from stability studies utilizing material from emergency supply, process performance qualification, clinical and one non-clinical lot of drug product. The stability data generated to date on the emergency supply and process performance qualification lots also support an additional storage condition at -20 ± 5°C for up to 2 weeks, as well as short term storage at 5± 3°C for up to one month (within the 6 month shelf life).

Drug product stability lots, from multiple global manufacturing sites, have been enrolled in stability programs and are being monitored in accordance with the approved protocols. All testing to date has been performed using analytical methodology and phase appropriate specifications in place at time of testing. The analytical procedures used in the stability programs were developed to monitor the composition, strength, purity, safety and general quality attributes of the drug product.

3.2.P.8.1.1. Drug Product Shelf Life at Recommended Storage Temperature

The initial shelf life of the BNT162b2 is 6 months when stored at the long term storage condition of -90 to -60 °C. The shelf life claim is based on up to 9 months of available stability data for clinical and non-clinical drug product lots and up to 6 months of available stability data for the emergency supply and process performance qualification lots, along with scientific rationale and the understanding of the mRNA platform. All drug product lots enrolled in the stability studies are considered to be predictive of the stability of the commercial materials based on comprehensive comparability assessments performed during development.

Additionally, the stability data generated to date on the emergency supply and process performance qualification lots also support an additional storage condition at -20±5 °C for up to 2 weeks, as well as short term storage at 5± 3°C for up to one month (within the 6 month shelf life). This is based on current available stability data for the accelerated conditions of -20±5 °C and 5± 3°C on emergency supply and process performance qualification lots.

3.2.P.8.1.1.1. In-use Period of Drug Product

The initial in-use period for the thawed, undiluted vial is room temperature for not more than 2 hours (Section 3.2.P.2.6 Compatibility). Formal thermal cycling stability studies have been initiated on both emergency use lots and PPQ lots in order to further support the in-use period. Available data from these studies is provided in Section 3.2.P.8.3 Thermal Stress and Cycling. The in-use shelf life of undiluted and diluted vials is defined in Section 3.2.P.2.6 Compatibility.

3.2.P.8.1.2. Stability Batches and Studies

The stability program is designed to follow ICH guidelines for stability of drug product (ICH Guideline Q1A: Stability Testing of New Drug Substances and Products; ICH Guideline Q5C: Quality of Biotechnological Products, Stability Testing of Biotechnological/Biological

Products). To date, thirteen process performance qualification lots (with one additional PPQ lot being placed on a thermal cycling stability study only), eight emergency supply lots, seven clinical lots and one non-clinical lot lots have been placed on stability and stored under long term, accelerated, and thermal stress conditions. The drug product lots placed on stability, to date, were packaged in commercial glass vials or glass vials representative of commercial packaging (for early non-clinical and clinical drug product studies).

Both the clinical and non-clinical drug product lots manufactured by Polymun Scientific using the BNT162b2 construct are considered to be predictive of the stability of the commercial materials based on comprehensive comparability assessments performed during development. The emergency supply lots were manufactured using the commercial process. Therefore, the clinical and non-clinical drug product lots manufactured by Polymun Scientific, as well as the emergency supply lots, are considered predictive of the stability of the commercial materials.

A summary of all drug product lots on stability studies and current available stability data are shown in Table 3.2.P.8.1-1. At this time, stability studies are on-going. Data from these studies will be used to confirm the initial shelf life of the drug product. Further information on confirmation and extension of the drug product shelf life is discussed in Section 3.2.P.8.1.7 Shelf Life and Conclusions.

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
EN6199 (Pfizer, Kalamazoo, Line (b) (4)	Stability, Emergency Supply[a], Process performance qualification	February 2021	Long Term	-90 to -60 °C	1 month	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	1 month	On-going
			Accelerated	5 ± 3 °C	1 month	On-going
EL3249 (Pfizer, Kalamazoo, Line (b) (4)	Stability, Clinical, Emergency Supply[a], Process performance qualification	December 2020	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
			Thermal Cycling	Thermal Cycling: 1 week at -90 to -60°C , followed by 2 weeks at -20 ± 5 °C, 4 weeks at 2 to 8°C and 1 week at 25 ± 2 °C/60 ± 5% RH.	8 weeks	Complete
EL9266 (Pfizer, Kalamazoo, Line (b) (4)	Stability, Emergency Supply[a], Process performance qualification	February 2021	Thermal Cycling	Thermal Cycling: Ultra frozen vials are placed at -20 ± 5 °C for 4 weeks and then moved to 2 to 8°C for 12 weeks. Samples will be pulled for testing every 2 weeks throughout protocol.	8 weeks	On-going
EL9267 (Pfizer, Kalamazoo, Line (b) (4)	Stability, Emergency Supply[a], Process performance qualification	January 2021	Long Term	-90 to -60 °C	1 month	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	1 month	On-going
			Accelerated	5 ± 3 °C	1 month	On-going
EL3248 (Pfizer, Kalamazoo, Line (b) (4)	Stability, Clinical, Emergency Supply[a], Process performance qualification	December 2020	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	1 month	Complete
EM4965 (Polymun Scientific/Pfizer, Puurs)	Stability, Emergency Supply[a], Process performance qualification	February 2021	Long Term	-90 to -60 °C	1 month	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	1 month	On-going
			Accelerated	5 ± 3 °C	1 month	On-going
EL7834 (Polymun Scientific/Pfizer, Puurs	December 2020	Stability, Emergency Supply[a], Process	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
		performance qualification	Thermal Cycling	Thermal Cycling: 1 week at -90 to -60°C followed by 4 weeks at -20 ± 5 °C and then 4 weeks at 2 to 8°C. and 1 week at 25 ± 2 °C/60 ± 5% RH.	10 weeks	Complete
			Photostability	Dark Control and Light Exposed		Complete
EN1195 (mibe/Pfizer, Puurs)	Stability, Emergency Supply[a], Process performance qualification	March 2021	Long Term	-90 to -60 °C	1 month	On-going
			Accelerated	-20 ± 5 °C	1 month	On-going
			Accelerated	5 ± 3 °C	1 month	On-going
			Thermal Cycling	Thermal Cycling: Ultra frozen vials are placed at -20 ± 5 °C for 4 weeks and then moved to 2 to 8°C for 12 weeks. Samples will be pulled for testing every 2 weeks throughout protocol.	6 weeks	On-going
EK4242 (mibe/Pfizer, Puurs)	Stability, Emergency Supply[a], Process performance qualification	December 2020	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
			Thermal Cycling	Thermal Cycling: 1 week at -90 to -60°C followed by 4 weeks at 2 to 8°C	5 weeks	Complete
EP2166 (Pfizer, Puurs)	Stability, Emergency Supply[a], Process performance qualification	January 2021	Long Term	-90 to -60 °C	2 months	On-going
			Accelerated	-20 ± 5 °C	2 months	On-going
			Accelerated	5 ± 3 °C	2 months	On-going
EL8713 (Pfizer, Puurs)	Stability, Emergency Supply[a], Process performance qualification	January 2021	Long Term	-90 to -60 °C	2 months	On-going
			Accelerated	-20 ± 5 °C	2 months	On-going
			Accelerated	5 ± 3 °C	2 months	On-going
EM6950 (Pfizer, Puurs)	Stability, Emergency Supply[a], Process performance qualification	January 2021	Long Term	-90 to -60 °C	2 months	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	2 months	On-going
			Accelerated	5 ± 3 °C	2 months	On-going
EL8723 (Pfizer, Puurs)	Stability, Clinical, Emergency Supply[a], Process performance qualification	January 2021	Long Term	-90 to -60 °C	2 months	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	2 months	On-going
			Accelerated	5 ± 3 °C	2 months	On-going
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	1 month	Complete

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
			Thermal Cycling	Thermal Cycling: Ultra frozen vials are placed at -20 ± 5 °C for 4 weeks and then moved to 2 to 8°C for 12 weeks. Samples will be pulled for testing every 2 weeks throughout protocol.	8 weeks	On-going
EL1491 (Pfizer, Puurs)	Stability, Emergency Supply[a], Clinical, Process performance qualification	December 2020	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
EH9899 Pfizer, Kalamazoo)	Stability, Emergency Supply[a]	November 2020	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
EJ1688 (mibe/Pfizer, Puurs)	Stability, Emergency Supply[a]	November 2020	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
EK1768 (Polymun Scientific/Pfizer, Puurs	November 2020	Stability, Emergency Supply[a], Clinical inventory	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
			Thermal Cycling	Thermal Cycling: 2 weeks at -90 to -60°C followed by 4 weeks at -20 ± 5 °C and then 8 weeks at 2 to 8°C. Samples will be pulled for testing every 2 weeks throughout protocol.	14 weeks	Complete
EJ1686 (Polymun Scientific/Pfizer, Puurs)	November/ December 2020	Stability, Emergency Supply[a], Clinical inventory	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
			Thermal Cycling	Thermal Cycling: 2 weeks at -90 to -60°C followed by 4 weeks at -20 ± 5 °C and then 8 weeks at 2 to 8°C. Samples will be pulled for testing every 2 weeks throughout protocol.	14 weeks	Complete
EJ1685	November 2020		Long Term	-90 to -60 °C	3 months	On-going

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
(Polymun Scientific/Pfizer, Puurs)		Stability, Emergency Supply[a], Clinical inventory	Accelerated	-60 to -30 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
EJ0553 (Polymun Scientific/Pfizer, Puurs)	November 2020	Stability, Emergency Supply[a], Clinical inventory	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-60 to -30 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
EE8493 (Polymun Scientific/Pfizer, Puurs)	September 2020	Stability, Emergency Supply[a], Clinical inventory	Long Term	-90 to -60 °C	6 months	On-going
			Accelerated	-60 to -30 °C	6 months	On-going
			Accelerated	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	1 month	Complete
EE8492 (Polymun Scientific/Pfizer, Puurs)	September 2020	Stability, Emergency Supply[a]	Long Term	-90 to -60 °C	6 months	On-going
			Accelerated	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
EE3813[c] (Polymun Scientific/Pfizer, Puurs)	August 2020	Stability, Clinical	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
ED3938[d] (Polymun Scientific/Pfizer, Puurs)	August 2020	Stability, Clinical inventory	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
BCV40720-C (Polymun Scientific)	August 2020	Stability, Clinical	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
BCV40720-A	August 2020	Stability, Clinical	Long Term	-70 ± 10 °C	6 months	Complete

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
(Polymun Scientific)			Accelerated	5 ± 3 °C	3 months	Complete
BCV40620-E (Polymun Scientific)	July 2020	Stability, Nonclinical	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
BCV40620-A (Polymun Scientific)	July 2020	Stability, Clinical	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
BCV40420-A (Polymun Scientific)	May 2020	Stability, Clinical	Long Term	-70 ± 10 °C	9 months	On-going
			Accelerated	-40 ± 5 °C	9 months	On-going
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C	4 months	Complete
CoVVAC/270320 (Polymun Scientific)	March 2020	Stability, non-clinical toxicology[b]	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	-40 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	6 months	Complete

a. Emergency supply designation applies to US market.
b. -40 °C study started in April 2020.
c. This lot number is equivalent to BCV40820-P
d. This lot number is equivalent to BCV40720-P.
RH = Relative Humidity

3.2.P.8.1.3. Protocol for Testing at the Long Term Condition (-90 to -60°C)

Vials from drug product lots were stored at the recommended storage condition of -90 to -60 °C. Testing is currently being performed on thirteen PPQ lots and eight emergency supply lots according to the protocol indicated in Table 3.2.P.8.1-2.

Additionally, testing at -70 ± 10 °C is being performed on seven clinical lots and one non-clinical lot according to the protocol indicated in Table 3.2.P.8.1-3.

Table 3.2.P.8.1-2. Protocol for BNT162b2 DP at the Long Term Condition of -90 to -60°C

Analytical Procedure	Test Interval [abe]
Appearance (Visible)	0, 1W[f], 2W, 1M, 2M, 3M, 6M, 9M, 12M, 18M, 24M
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	
Subvisible Particles	0, 3M[d], 6M, 12M, 18M, 24M
Container Closure Integrity Test	0, 12M, 24M[c]
Endotoxin	0, 12M, 24M [c]
Sterility	0, 12M, 24M

a. Testing not performed at the 1W, 2W or 2M timepoint for lot EE8493, EJ0553, EL3249, EL3248, EL7834, EK4242 and EL1491.
b. Testing not performed at the 2M time point for lots EH9899, EJ1688, EK1768, EJ1686 and EJ1685.
c. Being performed at 3 and 6M time points for EE8493, EE8492 and EJ0553.
d. Being performed at 3 time points for EE8493, EE8492 and EJ0553.
e. Testing not performed at the 1W or 2W timepoint for lot EN1195
f. 1W testing performed on lots EH9899, EJ1688, EK1768, EJ1686 and EJ1685
W = Week, M = Month, LNP = Lipid Nanoparticle

Table 3.2.P.8.1-3. Protocol for BNT162b2 Early Clinical and Non-clinical and Stability DP at the Long Term Condition of -70 ± 10°C

Analytical Procedure	Test Interval (months) [abd]
Appearance (Visible & Visible Particles)	0, 1, 3, 6, 9, 12, 18, 24
LNP Size	
LNP Polydispersity	
RNA Encapsulation	
RNA Content	
ALC-0315 Content	
ALC-0159 Content	
DSPC Content	
Cholesterol Content	
RNA Integrity	
Subvisible Particles	0, 12, 24
pH	
Sterility[c]	0, 24

a. For BNT162b2 lot BCV40420-A, a 4 month time point was added and tested
b. For BNT162b2 lot CoVVAC/270320, a 2 week and 2 month time point were tested. Study ends at 6 month time point.
c. Sterility testing not performed on non-clinical lot CoVVAC/270320.
d. For BNT162b2 lots BCV40620-A, BCV40620-E, BCV40720-A, BCV40720-C, BCV40720-P & BCV40820-P, only testing on 0, 1, 3 and 6 months is being performed. Sterility is being performed on 6M end point rather than 24M for this lot.

3.2.P.8.1.4. Protocol of Testing at the Accelerated Condition

To study the effects of temporary excursions above the recommended storage temperature, drug product is being stored under the accelerated conditions of -60 to -30 °C, -40 ± 5°C, -20 ± 5 °C and 5 ± 3 °C. Stability data obtained from the accelerated storage conditions are also presented in support of the shelf life claim.

Testing at -60 to -30 °C is currently being performed on five process performance qualification and three emergency supply lots according to the protocol indicated in Table 3.2.P.8.1-4.

Additionally, testing at -40 ± 5 °C is currently being performed on one clinical lot and one non-clinical lot according to the protocol indicated in Table 3.2.P.8.1-5.

Table 3.2.P.8.1-4. Protocol for BNT162b2 DP at the Accelerated Condition of -60 to -30°C

Analytical Procedure	Test Interval [ab]
Appearance (Visible)	0, 1M, 3M, 6M, 12M, 18M, 24M
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	
Subvisible Particles[c]	6M, 12M, 18M, 24M

a. Testing not performed at the 12M, 18M and 24M timepoint for emergency supply lot EE8493, EJ0553 and EJ1685.
b. 6M, 12M, 18M and 24M only time points being performed on PPQ lots EN6199, EL9267, EM4965, EM6950, and EL8723
c. Testing being performed on PPQ lots only as well as 6M time point for emergency supply lot EE8493
W = Week, M = Month, LNP = Lipid Nanoparticle

Table 3.2.P.8.1-5. Protocol for BNT162b2 DP at the Accelerated Condition of -40 ± 5°C

Analytical Procedure	Test Interval (months) [a]
Appearance (Visible & Visible Particles)	0, 1, 2, 3, 6, 9, 12, 18, 24
LNP Size	
LNP Polydispersity	
RNA Encapsulation	
RNA Content	
ALC-0315 Content	
ALC-0159 Content	
DSPC Content	
Cholesterol Content	
RNA Integrity	
pH	0, 12, 24
Subvisible Particles	
Sterility[b]	0, 24

a. For BNT162b2 lot BCV40420-A, a 4 month time point was added and tested
b. For BNT162b2 lot CoVVAC/270320, bioburden is being tested at final time point

Testing at -20 ± 5 °C is currently being performed on thirteen process performance qualification lots and eight emergency supply lots according to the protocol indicated in Table 3.2.P.8.1-6.

Table 3.2.P.8.1-6. Protocol for BNT162b2 DP at the Accelerated Condition of -20 ± 5°C

Analytical Procedure	Test Interval [abc]
Appearance (Visible)	0, 1W, 2W, 1M, 2M, 3M, 6M
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	
Subvisible Particles[d]	0, 6M

a. 1W testing performed on emergency supply lot EE8492 only.
b. Testing not performed at the 1W, 2W or 2M time point for emergency supply lot EE8493, EJ0553, EJ1685, EJ1686, and EK1768 or process performance qualification lots EL1491, EK4242, EL7834, EL3248, and EL3249.
c. Testing not performed at the 1W or 2W time point for emergency supply lots EJ1688 and EH9899 and process performance qualification lot EN1195.
d. Testing not performed on emergency supply lots EJ1685, EJ1686 and EK1768.
W = Week, M = Month, LNP = Lipid Nanoparticle

Testing at 5 ± 3 °C is currently being performed on thirteen process performance qualification lots and eight emergency supply lots according to the protocol indicated in Table 3.2.P.8.1-7.

Additionally, testing at 5 ± 3 °C is currently being performed on seven clinical lots and one non-clinical lot according to the protocol indicated in Table 3.2.P.8.1-8.

Table 3.2.P.8.1-7. Protocol BNT162b2 DP at the Accelerated Condition of 5 ± 3°C

Analytical Procedure	Test Interval [abcd]
Appearance (Visible)	0, 1W, 2W, 1M, 2M, 3M, 6M
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	
Subvisible Particles[e]	0, 6M

a. 1W testing performed on emergency supply lots EE8492, EJ1685, EJ1686, EK1768, EJ1688 and EH9899 only.
b. 1M, 3M and 6M testing only performed on process performance qualification lots EL3249, EL3248, EL7834, EN1195, EK4242 and EL1491.
c. 2M and 6M testing not perfomed on emergency supply lots EH9899, EJ1688, EK1768, EJ1686, EJ1685.
d. 1M and 3M testing only performed on emergency supply lots EJ0553 and EE8493. Emergency supply lot EE8492 ends at 3M time point.
e. Testing not performed on emergency supply lots EJ0553, EJ1685, EJ1686, EK1768, EJ1688 and EH9899.
W = Week, M = Month, LNP = Lipid Nanoparticle

Table 3.2.P.8.1-8. Protocol for BNT162b2 DP Manufactured by Polymun Scientific at the Accelerated Condition of 5 ± 3°C

Analytical Procedure	Test Interval (months)[abd]
Appearance (Visible & Visible Particles)	0, 1, 2, 3, 6
LNP Size	
LNP Polydispersity	
RNA Encapsulation	
RNA Content	
ALC-0315 Content	
ALC-0159 Content	
DSPC Content	
Cholesterol Content	
RNA Integrity	
pH	0, 6 [c]

a. For BNT162b2 lot BCV40420-A, a 4 month time point was added and tested
b. For BNT162b2 lot CoVVAC/270320, testing was also performed at the 2 week and 6 week time points
c. pH testing not performed on non-clinical lot CoVVAC/270320
d. Study ends at the 3M time point for BNT162b2 lots BCV40820-P, BCV40720-P, BCV40720-C, BCV40720-A, BCV40620-E and BCV40620-A. pH performed on the final 3M time point.

3.2.P.8.1.5. Protocol for Testing at the Thermal Stress Conditions

To study the effects of temporary excursions above the recommended storage temperature, drug product is being stored under thermal stress conditions at 25 ± 2 °C/60 ± 5% RH and 30 ± 2 °C/65% ± 5 RH and tested per the protocols indicated in Table 3.2.P.8.1-9 and Table 3.2.P.8.1-10 for emergency supply lots (lot EE8493 only placed on 30 ± 2 °C/65% ± 5 RH stability and lots EE8493, EJ0553, EJ1685, EJ1686,EK1768, EH9899 and EJ1688 placed on 25 ± 2 °C/60 ± 5% RH stability). Process performance qualification lots EL8723 and EL3248 were also each placed on formal stability according to the protocols indicated in Table 3.2.P.8.1-9 and Table 3.2.P.8.1-10.

Additionally, testing at 25 ± 2 °C is currently being performed on one clinical lot according to the protocol indicated in Table 3.2.P.8.1-11.

Table 3.2.P.8.1-9. Protocol for BNT162b2 DP at the Thermal Stress Condition of 25 ± 2°C/60 ± 5% RH

Analytical Procedure	Test Interval[ab]
Appearance (Visible)	0, 1W, 2W, 1M
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	

a. 1W timepoint not performed on lot EE8493.
b. 3W testing also performed on PPQ lot EL3248
W = Week, M = Month, LNP = Lipid Nanoparticle

Table 3.2.P.8.1-10. Protocol for BNT162b2 DP at the Thermal Stress Condition of 30 ± 2°C/65 ± 5% RH

Analytical Procedure	Test Interval[ab]
Appearance (Visible)	0, 1W, 2W, 1M
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	

a. 1W timepoint not performed on lot EE8493.
b. 3W testing also performed on PPQ lot EL3248
W = Week, M = Month, LNP = Lipid Nanoparticle

Table 3.2.P.8.1-11. Protocol for BNT162b2 DP at the Thermal Stress Condition of 25 ± 2°C

Analytical Procedure	Test Interval (months)
Appearance (Visible & Visible Particles)	0, 0.5, 1, 2, 3
LNP Size	
LNP Polydispersity	
RNA Encapsulation	
RNA Content	
ALC-0315 Content	
ALC-0159 Content	
DSPC Content	
Cholesterol Content	
RNA Integrity	
pH	0, 3

Thermal cycling studies are in progress for emergency supply lots EK1768 and EJ1686 according to the protocols indicated in Table 3.2.P.8.1-12. Thermal cycling studies are also in progress for process performance qualification lots according to the protocols indicated in Table 3.2.P.8.1-13 through Table 3.2.P.8.1-16.

Table 3.2.P.8.1-12. Protocol for BNT162b2 Emergency Supply DP Thermal Cycling Studies (Lots EK1768 and EJ1686)

Thermal Cycling Conditions: - Day 0, all inventory placed at -90 to -60°C for 2 weeks - At T=2weeks, samples pulled for testing and all other inventory transferred to -20 ± 5°C for 4 weeks. Samples will be pulled and testing will occur at the 2 and 4 week time points while at the -20 ± 5°C condition (week 4 and 6 of study). - At T=6 weeks, all remaining inventory will be transferred to 2 to 8°C for 8 weeks. Samples will be pulled and testing will occur at the 2, 4, 6 & 8 week time points while at the 2 to 8°C condition (week 8, 10, 12 & 14 of study).	
Analytical Procedure	**Test Interval (weeks) [a]**
Appearance (Visible)	0, 2, 4, 6, 8, 10, 12, 14
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	

a. Thermal cycling being initiated for lots EK1768 and EJ1686

Table 3.2.P.8.1-13. Protocol for BNT162b2 PPQ DP Thermal Cycling Studies (Lots EL8723, EN1195 and EL9266)

Thermal Cycling Conditions: - Day 0, all inventory (previously frozen to ultra cold temperatures of -90 to -60°C after manufacture) placed at -20 ± 5°C for 4 weeks - At T=4 weeks, samples pulled for testing and all other inventory transferred to 2 to 8°C for 12 weeks.	
Analytical Procedure	**Test Interval (weeks)**
Appearance (Visible)	0, 2, 4, 6, 8, 10, 12, 14, 16
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	

Table 3.2.P.8.1-14. Protocol for BNT162b2 PPQ DP Thermal Cycling Studies (Lot EL3249)

Thermal Cycling Conditions: - Day 0, all inventory placed at -90 to -60°C for 1 week - At T=1 week, inventory transferred to -20 ± 5°C for 2 weeks. - At T=3 weeks, samples pulled for testing and all remaining inventory transferred to 2 to 8°C for 4 weeks. - At T=7 weeks, samples pulled for testing and all remaining inventory transferred to 25 ± 2°C/60 ± 5%RH for 1 week	
Analytical Procedure	**Test Interval (weeks)**
Appearance (Visible)	0, 3, 4, 5, 6, 7, 8
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	

Table 3.2.P.8.1-15. Protocol for BNT162b2 PPQ DP Thermal Cycling Studies (Lot EK4242)

Thermal Cycling Conditions: - Day 0, all inventory placed at -90 to -60°C for 1 week - At T=1 week, all other inventory transferred to 2 to 8°C for 4 weeks, with testing occurring weekly while at 2 to 8°C	
Analytical Procedure	**Test Interval (weeks)**
Appearance (Visible)	0, 2, 3, 4, 5
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	

Table 3.2.P.8.1-16. Protocol for BNT162b2 PPQ DP Thermal Cycling Studies (Lot EL7834)

Thermal Cycling Conditions: - Day 0, all inventory placed at -90 to -60°C for 1 week - At T=1 week, inventory transferred to -20 ± 5°C for 4 weeks. - At T=5 weeks, samples pulled for testing and all remaining inventory transferred to 2 to 8°C for 4 weeks. - At T=9 weeks, samples pulled for testing and all remaining inventory transferred to 25 ± 2°C/60 ± 5%RH for 1 week	
Analytical Procedure	**Test Interval (weeks)**
Appearance (Visible)	0, 3, 5, 6, 7, 8, 9, 10
Appearance (Visible Particulates)	
(b) (4)	
Dynamic Light Scattering (LNP Size)	
Dynamic Light Scattering (LNP Polydispersity)	
Fluorescence Assay (RNA Encapsulation)	
Fluorescence Assay (RNA Content)	
HPLC-CAD (ALC-0315 Content)	
HPLC-CAD (ALC-0159 Content)	
HPLC-CAD (DSPC Content)	
HPLC-CAD (Cholesterol Content)	
Cell-based Flow Cytometry (In vitro expression)	
Capillary Gel Electrophoresis (RNA Integrity)	

3.2.P.8.1.6. Summary of Stability Data

3.2.P.8.1.6.1. Summary of Stability Data at the Long Term Storage Condition (-90 to -60 °C)

Results from stability studies on BNT162b2 DP stored at the long term condition of -70 ± 10 °C are currently available for seven clinical lots and one non-clinical lot of BNT162b2 material. Results from stability studies on BNT162b2 DP stored at the long term condition of -90 to -60 °C are also currently available for process performance qualification and emergency use lots. All results are provided in Section 3.2.P.8.3 Long-Term.

Up to 9 months of data are currently available for the lots manufactured by Polymun Scientific stored at the long term condition of -70 ± 10 °C. All data remained within the clinical acceptance criteria in place at the time of testing through the nine month time point for clinical lots BCV40420-A, through the 6 month time point for clinical lots BCV40620-A, BCV40620-E, BCV40720-A, BCV40720-C, BCV40720-P and BCV40820-P and through the 6 month time point for non-clinical lot CoVVAC/270320 (study has completed). Overall, the data indicate that there have been no significant changes in terms of quality, purity, or strength for the drug product.

Thirteen process performance qualification and eight emergency lots of emergency have been placed on formal stability at the long term condition of -90 to -60 °C, with up to 6 months of data available at this time. Overall, the data generated to date indicate that there have been no significant changes in terms of quality, purity, or strength for the drug product.

3.2.P.8.1.6.2. Summary of Stability Data at the Accelerated Storage Condition

Accelerated -40 ± 5 ℃ Stability

Results from stability studies on BNT162b2 DP stored at the accelerated condition of -40 ± 5 °C are presented for one clinical lot and one non-clinical lot. Results are provided in Section 3.2.P.8.3 Accelerated. All data remained within the clinical acceptance criteria in place at the time of testing through the nine month time point for clinical lot BCV40420-A and through the 3 month time point for non-clinical lot CpVVAC/270320. The -40 ± 5 °C accelerated condition provides additional supportive data for the long-term storage under recommended condition and supports temporary temperature excursions from the recommended storage condition.

Accelerated -60 to -30 ℃ Stability

Three lots of emergency supply drug product have been placed on formal stability at the accelerated condition of -60 to -30 °C, with up to six months of stability data currently available at this time for one lot and 3 months of available data for the other two. Five performance qualification lots have also been enrolled in formal stability programs at the -60 to -30 °C condition with release data available at this time. Results are provided in Section 3.2.P.8.3 Accelerated. All data generated to date remained within the acceptance criteria in place at the time of testing, as well as the proposed commercial specifications, through the 6 month time points and provide additional supportive data for the long-term storage under recommended condition.

Accelerated -20 ± 5 ℃ Stability

Results from stability studies on BNT162b2 DP stored at the accelerated condition of -20 ± 5 °C are presented for thirteen process performance qualification lots and eight emergency supply lots. Results are provided in Section 3.2.P.8.3 Accelerated. Up to six months of data are currently available for emergency supply lots EE8492 and EE8493, with the others having up to 3 months of data currently available. Up to three months of data are available for the process performance qualification lots. All data generated to date were also within the stated specifications at the accelerated condition of -20 ± 5°C through at least the 1 month time point. Lot EE8493 was out of specification at the 3 and 6 month time points and lot EK4242 was out of specification at the 3 month time point for (b) (4) at the accelerated -20 ± 5°C condition. The -20 ± 5 °C accelerated condition provides additional supportive data for the long-term storage under recommended condition, supports temporary temperature excursions from the recommended storage condition, and supports storage of the drug product for up to 1 month at -20 ± 5 °C.

Accelerated 2 to 8 ℃ Stability

Results from stability studies on BNT162b2 DP stored at the accelerated condition of 5 ± 3 °C are presented for seven clinical lots, one non-clinical lot, eight emergency supply lots and thirteen process performance qualification lots. Results are presented in Section 3.2.P.8.3 Accelerated.

Up to six months of data are currently available for clinical and th enon-clinical lots manufactured by Polymun Scientific. Up to three months of data are also currently available for emergency supply lots and for process performance qualification lots.

(b) (4) was out of clinical specification at the 3, 4 and 6 month time points for clinical drug product lot BCV40420-A. The two month time point for clinical drug product lots BCV40720-A and BCV40720-C were out of specification for (b) (4), as well as the 3 months time point for clinical drug product lot BCV40420-A (but within specifications at the 3 month time point for lot BCV40720-A and at the 4 and 6 months time points for lot BCV40420-A). (b) (4) was also out of the clinical specifications at the 3 month time point for clinical lot BCV40720-P. Clinical lots BCV40620-A, BCV40620-E and BCV40820-P were within all specifications in place at the time of testing through the 3 month time point (studies have completed).

Up to 3 months of data are currently available for the emergency supply and process performance qualification lots. The stability results at the accelerated condition of 5 ± 3°C are summarized in Table 3.2.P.8.1-17. All lots were within the stated specifications through at least the one month time point with the exception of EH9899 and EL3248. Lot EH9899 and Lot EL3248 were both manufactured using a (b) (4) (b) (4) using the original process, (b) (4) process revision. In addition, lot EL3248 was released at (b) (4) (b) (4), a level now below the proposed commercial specification (b) (4), as discussed in Section 3.2.P.5.6 Justification of Specification(s) (modRNA). Both of these lots expire in 2021 (31MAR2021 for lot EH9899 and 30APR2021 for lot EL3248), prior to implementation of allowable storage at 5 ± 3°C for 31 days. All lots that meet the (b) (4) proposed commercial specification for (b) (4) and utilize the improved (b) (4) process for (b) (4), are within specification at all timepoints tested to date, which are 1M for some lots and 2M for other lots. In addition, Section P.5.6 Justification of Specification(s) (modRNA) presents the trend analysis data for drug product stability lots that both meet the tightened release acceptance criterion and are manufactured using (b) (4) either from an updated (b) (4) process or from (b) (4). These data demonstrate that drug product stored at 5 ± 3°C for 31 days meet the specification of greater than or equal to (b) (4) (b) (4), based on the proposed (b) (4) commercial acceptance criteria at drug product release.

Table 3.2.P.8.1-17. Summary of Emergency Use and PPQ Drug Product Stability Results for 5C Storage

Lot #	ALC-0315 Lipid Source	RNA Integrity at Release (%)	Available 5 °C Data	5 °C Data Summary
EE8492	(b) (4)		3 months (complete)	Within specification through 1M
EE8493			3 months (complete)	Within specification through 1M
EJ0553			3 months (complete)	Within specification through 1M
EJ1685			3 months (complete)	Within specification through 3M
EJ1686			3 months (complete)	Within specification through 1M
EK1768			3 months (complete)	Within specification through 3M
EJ1688			3 months (complete)	Within specification through 3M
EH9899			3 months (complete)	(b) (4) out of specification at 2W and 3M
EL1491			3M (on-going)	Within specification through 3M
EL8723			2M (on-going)	Within specification through 2M
EM6950			2M (on-going)	Within specification through 2M
EL8713			2M (on-going)	Within specification through 2M
EP2166			2M (on-going)	Within specification through 2M
EK4242			3M (on-going)	Within specification through 1M
EN1195			1M (on-going)	Within specification through 1M
EL8734			3M (on-going)	Within specification through 3M
EM4965			1M (on-going)	Within specification through 1M
EL3248			3M (on-going)	(b) (4) out of specification at 1M and 3M
EL9267			1M (on-going)	Within specification through 1M
EL3249			3M (on-going)	Within specification through 1M
EN6199			1M (on-going)	Within specification through 1M

3.2.P.8.1.6.3. Summary of Stability Data at the Thermal Stress Storage Conditions

To support short term temperature excursions, drug product was exposed to the thermal stress condition of 25 ± 2 °C. Results for one clinical lot is presented in Section 3.2.P.8.3 Thermal – Stress and Cycling. There is currently up to four months of available data. All data remained within the clinical acceptance criteria in place at the time of testing through the two weeks (half month) time point. At the one month time point and beyond, drug product lot BCV40420-A was out of specification for (b) (4). Changes can be expected at

stressed stability conditions and does not impact the overall stability strategy for this material.

Process performance qualification and emergency supply lots have been exposed to the thermal stress conditions of 25 ± 2 °C/60 ± 5% RH and 30 ± 2 °C/65 ± 5% RH. There is up to one month of available data for process performance qualification and emergency supply lots presented in Section 3.2.P.8.3 Thermal – Stress and Cycling.

(b) (4)

(b) (4) Changes can be expected at stressed stability conditions and does not impact the overall stability strategy for this material. This stability data provides further support to the current in-use period stability.

(b) (4)

(b) (4) All other attributes remained within the specifications in place at the time of testing. Changes can be expected at stressed stability conditions and does not impact the overall stability strategy for this material. This stability data provides further support to the current in-use period stability.

3.2.P.8.1.6.4. Summary of Stability Data at the Thermal Cycling Storage Conditions

Two emergency supply drug product lots, EK1768 and EJ1686, have thermal cycling studies that have completed with 14 weeks of data available. These studies were performed to provide further support to the in-use period for the drug product. Results available through

the 14 week time points for emergency supply lots are presented in Section 3.2.P.8.3 Thermal – Stress and Cycling. All data generated to date remained within the acceptance criteria in place at the time of testing through the 14 week time points (completion of the studies).

Additionally, process performance qualification lots have thermal studies initated at this time to provide further support to the in-use period for the drug product. Results available to date for the process performance qualification lot thermal cycling studies are presented in Section 3.2.P.8.3 Thermal – Stress and Cycling. Lots EN1195, EL9266 and EL8723 are enrolled in the same thermal cycling study design and have up to 8 weeks of data available. Thermal cycling study for lot EL3249 and EL7834 have completed with 8 weeks of available data for EL3249 and 10 weeks for EL7834. Thermal cycling study for lot EK4242 has also completed, with up to 5 weeks of available stability data. (b) (4) (b) (4) all data generated to date remained within the acceptance criteria in place at the time of testing through the completion of the study. All other thermal cycling data also remained within the acceptance criteria in place at the time of testing through time points tested to date.

3.2.P.8.1.6.5. Summary of Photostability Stability in Drug Product Vials

One process validation drug product lot, EL8734, was subjected to the ICH photostability condition (option 2). Drug product vials were exposed to a light source that provides an overall illumination of not less than 1.2 million lux hours and an integrated ultraviolet energy of not less than 200 watt hours/m^2, per ICH Q1B. Dark control vials were wrapped in aluminum foil to prevent exposure to light. All samples were stored inverted, at 2 to 8 °C for the duration of the study, as it is not feasible to maintain the samples at the intended storage condition of -90 to -60 °C for this study and the 2 to 8 °C condition is considered a worse case exposure condition.

Results for both the dark control and the light exposed samples were within the specifications in place at the time of testing. (b) (4) (b) (4) (b) (4) all results generated were within the proposed commercial specifications.

3.2.P.8.1.7. Shelf Life and Conclusions

The initial shelf life for the BNT162b2 DP is 6 months when stored at the recommended temperature of -90 to -60 °C. Additionally, the stability data generated to date on the emergency use and process performance qualification lots also support an additional storage at -20 ± 5°C for up to 2 weeks as well as short term storage at 5± 3°C for up to one month (within the 6 month shelf life).

The initial shelf life is based on:

- Up to 6 months of current available stability data on emergency supply lots and process performance qualification lots at both the -90 to -60 °C intended storage condition, as well as the -20 ± 5°C storage condition, and up to 3 months at the 5± 3°C storage condition.

- Up to 9 months of current available stability data on seven lots of clinical drug product
- Up to 6 months of current available stability data on one lot of non-clinical drug product
- Up to 9 months of current available stability data on two clinical lots of BNT162b1 drug product
- Comprehensive comparability assessments performed during development.
- Understanding of the mRNA platform to support the initial shelf life

Additionally, the initial in-use period for the thawed, undiluted vial is room temperature for not more than 2 hours, which is further discussed in (Section 3.2.P.2.6 Compatibility).

These stability studies are currently on-going and data from these studies will be used to confirm the initial shelf life of the BNT162b2 DP, as well as extend the shelf life based on the acceptability of the data.

The shelf life will be extended beyond the 6 months initial shelf life, as data allows, at the intended storage condition of -90 to -60 °C and/or beyond the 2 weeks at the storage at -20 ± 5°C or 5± 3°C storage for up to one month using real time stability data on a minimum of three batches of commercially representative material.